HPV and HIV: Anogenital Disease

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Objectives

- Describe immune responses to HIV and HPV infections
- Review the patterns of HPV infection in HIV+ women
- Review the data on the evaluation of cervical dysplasia in HIV+ women
- Describe relation of HPV and anal cancer

HIV Viral Replication

- First step, HIV attaches to susceptible host cell.
  - Site of attachment is the CD4 antigen found on a variety of cells
    - helper T cells
    - macrophages
    - monocytes
    - B cells
    - microglial brain cells
    - intestinal cells
  - T cells infected later on.

HIV Viral Replication

- After a period of latency lasting up to 10 years viral replication is triggered and occurs at high rate.
- CD4 cells may be destroyed in the process, body attempts to replace lost CD4 cells, but over the course of many years body is unable to keep the count at a safe level.
- Destruction of large numbers of CD4 cause symptoms of HIV to appear with increased susceptibility to opportunistic infections, disease and malignancy.

HIV Viral Replication

- Methods of transmission:
  - Sexual transmission, presence of STD increases likelihood of transmission.
  - Exposure to infected blood or blood products.
  - Use of contaminated clotting factors by hemophiliacs.
  - Sharing contaminated needles (IV drug users).
  - Transplantation of infected tissues or organs.
  - Mother to fetus, perinatal transmission variable, dependent on viral load and mother's CD 4 count.

The Natural History of HPV Infection Suggests that Immunity is Effective

- Most HPV infections are cleared without clinical disease. When lesions develop, they regress after several months
- Individuals who have decreased cell mediated immunity (transplant recipients and patients with HIV) have an increased prevalence and persistence of HPV infections
- The humoral immune response accompanies papilloma regression, and is effective in preventing reinfection
- Immunity to HPV is effective but often delayed

HPV Immunology

- Most HPV infections are not apparent or regress, suggesting that the host's immune response is effective
- The HPV life cycle has evolved to evade the host's immune response, and HPV early proteins directly inhibit specific components of immunity
- Papilloma regression is mediated by a Th1 type cell mediated immune response with infiltration of macrophages and CD4+ cells
- Humoral immunity is protective

HIV and Cervical Cancer

- 1993: Cervical cancer as AIDS-defining illness in HIV+ women

- In high-risk urban setting, cervical cancer was the most common AIDS-related malignancy
  - High grade, advanced disease
  - Recurrent disease common
  - High death rate
- 6th most common AIDS-defining illness in women

Maiman et al, Obstet Gynecol 1997, 89:76-80

HPV and HIV: Cervical Disease

- Prevalence: ↑ Pap and Biopsy abnormalities
  - HIV+ 13-60%
  - HIV- 2-17%
- Incidence: ↑ in HIV+ women over 30 month follow-up (20 vs. 5%)
- Progression and regression:
  - ↑ progression rates in HIV+ women
  - ↓ regression rates in HIV+ women

Danso et al. International Journal of STD & AIDS 2006; 17:579-586

HPV in HIV + Women: WIHS Cohort

- High prevalence of HPV
  - 26% HIV - high risk women
  - **70% HIV + with CD4 < 200/mm^3**
- Multiple HPV types
  - 16% HIV - high risk women
  - **42% HIV + women**
- Abnormal cytology
  - 16% HIV - high risk women
  - **53% HIV + with CD4 < 200/mm^3**

Palefsky, Monogr Natl Cancer Inst 1998; 23:15-20

HIV positive women have higher rates of HPV and significant diversity

Our clinic in Jo'burg (191 women screened) Dr Masangu Mulongo IAS Conference, Durban 2016

Over 80% our women screened have an HR type of HPV

Two women had 8 different oncogenic types

Different types also 40% 16 then 56, 66

ZAMBIA- 85% had HR HPV types 52, 58

SIL in HIV + Women: Prevalence

- SIL: 30 – 50% prevalence
  - SIL in WIHS cohort *
    - HIV+ 17.4% (2.5% HSIL)
    - HIV- 3.5%
- Higher grade lesions
- Extensive involvement
- Multi-site involvement
- More aggressive disease

Maiman, Monogr Natl Cancer Inst 1998; 23:43-49
**Massad et al J AIDS Hum Retrovir 1999; 21:33-41.*

HIV / AIDS and Cervical Dysplasia Prevalence rates – higher

- USA -16.2% Dysplasia (LSIL 14.1%, HSIL 2.1%)
- 4% Dysplasia in HIV negative Massad et al AIDS 2004 18: 109-113
- Europe-26.5% Dysplasia (LSIL 19%, HSIL 7.5%) 7.5% in HIV negative Six etal AIDS 1998 12;(1047-1756)
- Brazil 26.7% Dysplasia (LSIL 21% HSIL 5.7%) personal communication Professor Breatriz Grinsztejn
- Zambia 76% Dysplasia (HSIL 33% 43% LSIL) Parham et al Gynecol Oncol 103 (1017-10220
- South Africa 51% Dysplasia (HSIL 18% and 23.5% LSIL) Firnhaber et al Cancer Causes Control epub 1 Dec 2009 HIV unknown status 26% Dysplasia Conje Int J Gynaecol Obstet 84:101-108

  South Africa --rural areas (unpublished confirmed reports of 60% HSIL)

Initial Results from a Multi-Country Cervical Cancer Screening Program for HIV-Infected Women

- Summary of study:
  - VIA/SVA for cervical cancer prevention in Côte d'Ivoire (n=7,538), Guyana (n=19,934) and Tanzania (n=7,449)
  - Services provided by trained nurses/midwives at HIV care and treatment sites and general health facilities
- Key results:
  - In all 3 countries, HIV-positive women were more likely to be VIA-positive than HIV-negative/unknown women
  - In all 3 countries, HIV-positive women who were VIA-positive were more likely to have large lesions (occupying >75% cervix) and therefore ineligible for cryotherapy
  - 85% of eligible women had same-day treatment with cryotherapy; of those who postponed, 48% did not return for treatment

Source: Anderson J, Lu E, Wysong M, Kibwana S, Estep D, Varallo J, Toure K, Giattas M, for Jhpiego.

Cervical Cancer: HIV + Women

- CDC / USPHS: Pap test x 2, then annual
- 2001 ASCCP Guidelines:
  - Referral to colposcopy for ASC-US+
- 2006 ASCCP Guidelines:
  - Management similar to HIV- women

SIL in HIV + Women: Management

- Use basic triage rules (ASCCP guidelines)
- All treatment options have higher failure rates than in HIV- women (correlates with CD4)
- Cryotherapy: Significantly high failure rates
  - Cryotherapy for low grade CIN
    - 48% HIV + recurred
    - 1 % HIV - recurred

SIL in HIV + Women: Treatment

- Excision > Ablation

  Loop / Cone > Cryo / Laser

- Confirmation of histology
  - ↓ correlation with biopsy grade
  - Evaluation of margins

SIL in HIV + Women: Other treatment options

- Recurrent High grade CIN:
  - Retreatment
  - Maintenance: Vaginal 5-FU*
    - ½ applicator every other week
    - ↓ recurrence rates ~ 40 ⇨ 20%
- Imiquomod (Aldara): little data, not for internal use

**Maiman et al (ACTG 200) Obstet Gynecol 1999;94:954-961.*

SIL and HIV: ? Invasion

- Most women recently infected with HIV
- Natural history of HPV is long (10-20 years)
- Most women are screened
- CIN 2-3 treated to prevent progression
- Development of SIL influenced by immune function

HIV and HPV: Effect of HAART?

- Conflicting reports: Limited positive effect
- Development of SIL influenced by immune function
- ↑ Regression of low grade lesions on HAART
- ? Progression to invasive disease
- ? Treatment may be more effective when on HAART
  - Fewer recurrences post-excisional therapy

HIV and HPV

- Goals of management

- Prevent Cancer!!!
- Treat High grade lesions

- Persistent low grade disease
  - May be acceptable
  - May be inevitable

HPV-related Lesions of the Cervix and Anal Canal

SIMILARITIES >> DIFFERENCES

HIV and Anal Cancer

- Anal transformation zone similar to cervical transformation zone
- High incidence HPV and HSIL is gay/bisexual men (HIV+ > HIV -)
- Increasing anal cancer in MSM
- Anal SIL in women?
  - HIV+ > HIV-
- Should we screen?

Anal Cancer and Cervical Cancer

- Common risk factors
  - Sexual intercourse
    - Vaginal
    - Anal
- Human papillomavirus infection
  - High-risk HPV
  - HPV 16 and 18

Squamous Cell Carcinoma: Cervix and Anus Cancer

- Caused by high-risk HPV types
- Associated with high grade SIL
- Arise in the transformation zone
- Morphologic similarity
  - Precursor lesions
  - Cancer